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Peri-operative anaphylaxis

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Peri-operative anaphylaxis is an important cause for mortality and morbidity associated with anaesthesia. The true incidence is unknown and is most likely under reported. Diagnosis can be difficult, particularly as a number of drugs are given simultaneously and any of these agents can potentially cause anaphylaxis. This review covers the clinical features, differential diagnosis and management of anaphylaxis associated with anaesthesia. The investigations to confirm the clinical suspicion of anaphylaxis and further tests to identify the likely drug(s) are examined. Finally the salient features of common and rare causes including non-drug substances are described.

Introduction, incidence, terminology

Serious allergic events occurring during anaesthesia and the peri-operative period are rare, but can rapidly evolve into life-threatening situations if not recognized and managed promptly.

The operating theatre is a unique clinical environment. Patients are exposed to numerous medications over a relatively short period of time, particularly during the induction phase of anaesthesia. General anaesthetics necessarily involve the administration of several drugs in rapid succession. Patients are also exposed to numerous non-drug substances, such as antiseptic skin preparations, intravenous colloids and latex. As a consequence, anaesthetists are more likely than most other physicians to witness and manage allergic reactions. The reported incidence of peri-operative anaphylaxis varies from 1 in 6000 [1] to 1 in 20 000 anaesthetics [2].

Given the random nature of these unexpected events, published data on peri-operative anaphylaxis largely take the form of individual case studies and small apparent case clusters. Anaphylaxis is potentially fatal, and there are consequently no prospective *in vivo* trials in human subjects. Over the past decade, retrospective information from anaesthetic-related allergy databases, notably from France [3], Norway [4], the United Kingdom [5], New Zealand and Australia [2,6] has produced a more coherent picture of the problem. Several clinical practice guidelines for the diagnosis and management of peri-operative anaphylaxis have been produced by groups considering available evidence, and using expert consensus where evidence is lacking [7,8].

Mechanisms of anaphylaxis

Allergic reactions are classified into four types according to Gell & Coombs [9–11]. Those causing concern during the immediate peri-operative period are usually of the anaphylactic type (type 1 reactions). Johansson *et al*. defined anaphylaxis as a 'severe, life-threatening, generalized or systemic hypersensitivity reaction' [12], a definition adopted by Harper *et al*. in their Practice Guidelines for the Association of Anaesthetists of Great Britain and Ireland [8].

Anaphylaxis occurs rapidly, systemically and can affect one or more organ systems. Underlying the pathophysiology of this process is the degranulation of mast cells or basophils and the release of preformed mediators including histamine, tryptase, carboxypeptidase A and proteoglycans [13–15]. Activation also results in the synthesis of arachnidonic acid metabolites and platelet activating factor (PAF) [16] and is followed by (usually 2–6 h later) the release of cytokines (e.g. tumour necrosis factor alpha (TNF-α), the result of increased gene expression [13, 17, 18]. It is these released mediators that play an important role in the pathophysiology of anaphylaxis and have an effect on a number of organ systems including cardiovascular (hypotension and arrhythmias), respiratory (bronchospasm and upper airway obstruction), skin (urticaria and angioedema) and bowels (abdominal cramps, nausea and vomiting) [15, 18] (see Table 1). Histamine contributes to these clinical features through triggering vasodilatation and increased vascular permeability [19]. Prostaglandin D_2 causes bronchoconstriction, pulmonary and coronary artery constriction and peripheral vasodilatation [20].

Table 1
Clinical features of anaphylaxis [7, 8, 28]

System	Range of symptoms
Skin	Urticaria, angioedema, generalized erythema,
Cardiovascular	Vasodilation, hypotension and shock, loss of vascular fluid via 'leaky capillaries' with localized or generalized swelling, cardiac dysrhythmias, pulseless electrical activity, ventricular fibrillation, ST changes and coronary vasospasm
Respiratory	Cough, bronchospam of varying degree, mucous plugging of bronchi, rhinitis, oedema of the upper airways with potential obstruction, pulmonary oedema, cyanosis
Gastro-intestinal	Abdominal cramps, nausea, vomiting, diarrhoea
Other	Disseminated intravascular coagulation, fibrinolysis

Leukotrienes and PAF contribute to the bronchoconstriction, myocardial depression and increased vascular permeability [21, 22]. TNF-α, with the release of chemokines, is thought to be important in the late phase response [23–25]. The mechanisms that trigger mast cell and basophil degranulation can be categorized into those that are mediated by IgE (anaphylactic) and those directly affecting these cells and are independent of IgE (anaphylactoid) [26]. The European Academy for Allergology and Clinical Immunology has proposed a new way of classifying these reactions, where all reactions are termed anaphylaxis with those mediated by IgE antibodies being referred to as IgE-mediated allergic anaphylaxis and those the result of a non-immunologic cause referred to as non-allergic anaphylaxis [12, 27, 28]. Clinically they are indistinguishable. In the context of peri-operative anaphylaxis common causes for non-allergic anaphylaxis include opiates and NSAIDs. The mechanism for this is not well understood. IgE mediated reactions are better characterized and involve the agent (e.g. antibiotic) cross-linking IgE molecules, specific for that agent, on the surface of basophils or mast cells. This triggers their degranulation and mediator release.

Presentation and differential diagnosis

The clinical presentation of anaphylaxis is varied. Some symptoms may not be appreciated in the unconscious subject. Many organ systems may be involved (Table 1). The severity of the reaction can vary from one which is barely noticeable and quite transient to one which is catastrophic and from which the patient cannot be resuscitated. In addition, the clinical picture varies between patients, with one patient showing entirely cardiovascular symptoms, whereas another patient might have predominantly respiratory manifestations. In the busy environment of an operating theatre, vigilance and a high level of suspicion are needed in order to recognize when a patient might have suffered an anaphylactic reaction, whose symptoms may exactly resemble side-effects of drugs or complications of surgery. Indeed, it is probable that the true rates of peri-operative anaphylaxis are higher than the reported levels due to the 'masking' action of these other events. Additionally, most individual symptoms of anaphylaxis have a more common aetiology, and diagnosis will often be made only after other likely causes have been excluded. Appropriate management must be initiated as early as possible during the reaction in order to stabilize the patient and produce the best outcome.

The route of administration of the allergen affects the clinical course of the reaction. The intravenous route tends to produce sudden reactions, whereas mucous membrane or skin exposure tends to lead to reactions of slower onset. Substances given by infiltration, such as marker dyes (e.g. patent blue V), have been documented to give protracted reactions refractory to treatment [29]. The same allergen given by different routes in the same patient can produce clinically different reactions.

Patient factors also influence the clinical picture of a reaction. Subjects who are usually asthmatic are more likely to have significant bronchospasm as part of any anaphylactic reaction [8]. Patients with significant cardiac disease are much less able to tolerate the haemodynamic perturbations produced by anaphylaxis than normal patients and are more likely to develop shock refractory to treatment [30]. Patients taking β-adrenoceptor blockers both release more anaphylactic mediators and are less able to mount a tachycardia in response to vasodilation, and are subsequently prone to develop more profound shock [31].

The clinical context in which anaphylaxis occurs can influence both the reaction itself, or mask it, making its diagnosis less obvious. Where intra-operative haemorrhage occurs and rapid infusion of intravenous colloid (e.g. substituted gelatines) is necessary, an allergic-type reaction to the colloid would appear initially to the anaesthetist as worsening haemorrhage and the infusion rate of the colloid might then be increased.

Neuraxial blockade, such as spinal and epidural anaesthesia, consistently produces hypotension by a direct action on spinal sympathetic fibres. This would normally be anticipated and managed as it occurred. If an allergic reaction to another drug (such as a prophylactic antibiotic) occurred simultaneously, it would initially be disguised by the anaesthetic-induced hypotension.

Myocardial ischaemia, ST changes and dysrhythmias may occur during anaphylaxis. The apparent clinical scenario might then be one of a patient with primary myocardial ischaemia, with resultant cardiac insufficiency. Treatment could be misdirected at the assumed primary problem. When later investigated, these patients might not even have coronary artery disease [32], although this scenario does seem more likely in patients who do. Changes

produced by anaphylactic mediators (reduced venous return, coronary vasospasm [33], tachycardia and reduced aortic root pressure) tend to reduce coronary blood flow. Similarly, wheezing or hypoxia might, in the first instance, be assumed to be due to asthma, a blocked endotracheal tube or even pneumothorax, rather than anaphylaxis.

Patients are usually fully draped for surgery, and any skin signs of an anaphylactic reaction may pass unnoticed. The development of urticaria (wheal and flare), angioedema (which may occur in the absence of urticaria) or generalized flushing occurring peri-operatively strongly corroborates a diagnosis of anaphylaxis. Patients with other signs of an allergic reaction should be uncovered to check for these cutaneous manifestations.

Initial management of peri-operative anaphylaxis

Early specific management of anaphylaxis appears to improve outcome and is directed at maintaining intravascular fluid volume, vascular tone and cardiac output. Updated Management Guidelines for Suspected Anaphylactic Reactions Associated with Anaesthesia have been compiled by a working party of the Association of Anaesthetists for Great Britain and Ireland and describe management in detail [8]. This guideline is outlined here. Anaesthetized patients already have intravenous access and are continuously monitored. An immediate assessment of airway and breathing should be made, bearing in mind that upper airway oedema could occur as the reaction develops.

All drugs given prior to the reaction should be stopped and an alternative used. Other potential trigger substances to which the patient has been exposed (e.g. latex, intravenous colloids or chlorhexidine) should be removed. A rapid judgement should be made about whether it is appropriate that surgery should continue.

Intravascular volume should be maintained in anticipation of vasodilation and fluid extravasation. The patients legs can be raised, and intravenous fluid commenced as soon as possible (e.g. Hartmanns solution, 0.9% saline, avoid colloids if these were given prior to the event) via a large bore cannula. Several litres may be required rapidly in an average adult. Epinephrine should be given intravenously (aliquots of 50 μg in an average adult), repeated until the patient responds. An infusion of epinephrine may be required if repeated doses are necessary. Cardiopulmonary resuscitation should be administered if necessary without delay.

Further management depends on the particular clinical presentation of the patient. Specific management for bronchospasm (e.g. salbutamol and aminophylline) may be necessary. Where hypotension is resistant to adrenaline, use of a specific vasoconstrictor such as metaraminol is suggested. In the Scandinavian Clinical Practice Guidelines, Kroigaard *et al*. further recommend the use of a norepinephrine infusion or incremental doses of vasopressin. Where the patient has taken β-adrenoceptor blockers, the use of increments of glucagon is suggested to overcome the effect of these [7]. Where anaphylaxis occurs in cardiac surgical patients, rapid institution of cardiopulmonary bypass may prove necessary, as this group are at high risk of becoming unresuscitatable [30].

As soon as the patient is more stable, a histamine H_1-receptor blocker (chlorphenamine) and hydrocortisone should be given intravenously [8]. It has been shown by the Danish Anaesthetic Allergy Centre that in fewer than a third of cases of peri-operative allergy does the managing anaesthetist correctly guess the precipitating agent. All cases will need to be followed up after the event in a specialist centre to avoid exposing the patient again [34].

If surgery needs to be continued (e.g. emergency procedure), the ongoing management of haemodynamic instability will be necessary. In addition, fibrinolysis has been documented after anaphylaxis. This may increase peri-operative bleeding significantly and De Souza *et al*. describe the use of tranexamic acid, an antifibrinolytic agent, to manage this [35].

In vitro testing for peri-operative anaphylaxis: Tests to confirm clinical suspicion of anaphylaxis

Histamine

Histamine is present within mast cells and basophils and released when they are activated. This can be from both allergic (IgE mediated) and non-allergic mechanisms. Histamine is difficult to measure and not routinely tested as part of the investigation of suspected anaphylaxis. It has a short half-life and plasma histamine needs to be measured within 30 min of the suspected anaphylaxis [36, 37]. It is not tested by many laboratories in the UK.

Tryptase

Tryptase is neutral serine protease, predominantly present in mast cells, with only minimal amounts present in basophils (<1%) [38]. There are two major forms of tryptase, α and β. β-tryptase is processed from a pro to mature form and is stored within secretory granules. The mature β-tryptase is released upon activation. α-tryptase is present as a pro form in mast cells and with the pro form of β-tryptase, released spontaneously [39]. Pro β-tryptase and α-tryptase give an indication of mast cell load and are elevated in mastocytosis. Most laboratories measure both α and β-tryptase together and do not discriminate pro and mature forms. Due to this lack of differentiation between the types of tryptase, a single raised level of tryptase will not be able to distinguish between increased mast cell load (e.g. mastocytosis) from a raised level due to anaphylaxis. Serum tryptase concentrations are at their highest at

peak of symptoms [40], then fall to a normal baseline. Therefore seeing a rise and fall in concentrations suggests this is due to degranulation (anaphylaxis), while a constantly raised concentration would indicate mastocytosis or other conditions associated with a raised total tryptase (e.g. acute myelocytic leukaemia and myelodysplastic syndromes [41]). To determine this difference in dynamics, more than one measurement of tryptase is needed. The recommended time points to measure tryptase are one immediately after resuscitation, one at 1–2 h and a baseline sample at 24 h or any time after this [28].

In the context of peri-operative anaphylaxis, a rise and fall of serum tryptase would confirm mast cell degranulation and the clinical suspicion of an anaphylactic reaction. Persistently elevated concentrations would fit with a high mast cell load and probable mastocytosis. This is also an important diagnosis in this context as such patients are at greater operative risk due to anaphylaxis [42–44].

Even with careful and timely measurement of tryptase, there are instances where a significant transient rise in tryptase is not detected, even when the clinical suspicion of anaphylaxis is high, or where further investigation has revealed a positive drug reaction [39,45,46]. Serum tryptase is usually not elevated without shock or hypotension [47]. Cases have been described where the tryptase does not rise but histamine does and testing for both increases diagnostic sensitivity [48]. This phenomenon may reflect the different kinetics of mast cell mediators. Carboxypeptidase A3 is released by activated mast cells but in patients with anaphylaxis, its serum concentrations do not always correlate with tryptase. Patients with anaphylaxis have been found to have elevated carboxypeptidase A3, independent of tryptase [47, 49]. Another explaination for the failure to detect a rise in tryptase could be the predominance of basophil degranulation during these reactions, as basophils contain only minimal amounts of tryptase. Research is currently looking at basogranulin, a basophil specific protein released on activation [50, 51]. Its measurement may explain the disparity between tryptase and histamine in some cases of anaphylaxis.

Tests to identify the causative agent

In vitro *tests*

Identifying the causative agent is important in the clinical work up of peri-operative anaphylaxis. Not only does this confirm clinical suspicion of a reaction, particularly if the tryptase is not raised, but also enables alternative agents to be chosen should further anaesthesia be required.

In vitro testing is convenient, but has its limitations, particularly poor sensitivity. The main assay available is directed at testing for specific IgE to the suspect drug. The basophil activation assays investigate both IgE mediated allergic and non-allergic anaphylaxis. However, these also are limited by their poor sensitivity.

Specific IgE

Anaphylactic reactions involve antigen specific IgE antibodies (sIgE) triggering mast cell or basophil degranulation. Previously a radioimmunoassay (Radio Allergo Sorbent Test (RAST)) was used [52, 53]. This has evolved with the current use of non-radioactive and more automated methods. Generally the test involves coupling the agent, e.g. drug to a solid phase such as nitrocellulose membrane, polymer such as sepharose or cellulose sponge (ImmunoCAP). The serum containing sIgE is added and allowed to bind to the drug. This is then detected using an anti IgE antibody and amount of bound sIgE quantified.

The availability of sIgE tests for the range of drugs and agents involved in peri-operative anaphylaxis is limited. Most UK laboratories use ImmunoCAP technology [54] (examples of sIgE available include penicillin V and G, amoxicillin, cefaclor, suxamethonium, chlorhexidine and latex). Recently introduced using this platform are tests for sIgE to quaternary ammonium morphine and pholocodine (ImmunoCAP allergen c260 and 261, respectively). Both are useful markers for sensitization to NMBAs and have a higher sensitivity than suxamethonium. In an evaluation study using patients known to be allergic to rocuronium both demonstrated high specificity (100%) and good sensitivity (88% and 86%, respectively) [55]. For other drugs, testing for sIgE has good specificity, but sensitivity tends to be poor (30–60% for suxamethonium [56] and 0–75% for penicillins [57]).

A study looking at fluctuations in sIgE to suxamethonium revealed no significant change in levels of sIgE taken around the time of anaphylaxis, compared with days or weeks later [58].

Basophil assays

Basophils are present in peripheral blood and although they represent a small proportion of peripheral blood leucocytes [59], they can be used in specific assays for allergy. By stimulating with the potential allergen (drug), mediators released can be directly measured as an indicator of degranulation (mediator release assays), e.g. measuring sulphidoleukotriene [60, 61]. Other assays look for changes to the molecules present on the surface of basophils as an indicator of activation. The molecules CD203c and CD63 are the main markers for activation used [62]. However others are also being assessed including intracellular phosphorylated p38MAPK [63]. These tests are showing promise and generally have good specificity, but they have poor sensitivity [64–67] and are currently not widely used.

Skin testing

Despite the developments in *in vitro* testing, skin and intradermal testing have better sensitivity and play an important role in the investigation of peri-operative anaphylaxis. Unlike sIgE measurement it is recommended that skin prick (SPT) and intradermal (IDT) testing should be done follow-

ing a 4–6 weeks delay to avoid false negative test results [7, 56, 68]. This is for theoretical reasons (possible mast cell depletion) and has yet to be demonstrated. SPT is performed by applying the agent to the skin and pricking the skin with a lancet. Positive (histamine) and negative controls (saline) are essential to correct interpretation of results and reading of the skin reaction should be at 15 to 20 min. If negative it should be followed by intradermal testing. Intradermal testing is more sensitive but less specific than SPT [69] and is performed by injecting 0.02 to 0.05 ml of drug.The skin is examined at 20 min to determine reactivity. The drugs used for testing are freshly prepared and diluted according to established guidelines. Generally intradermal testing is started at the lowest dilution first and if negative increased by 10-fold increments until an accepted non irritant dose is reached. Established concentrations of drugs that are normally non-reactive (highest acceptable dose to be used) have been published [7, 56, 70]

Challenge provocation testing

A drug provocation test (DPT) is used to diagnose immune and non-immune mediated drug reactions and provides a direct means of testing a suspect drug reaction on the index individual [71]. DPTs are considered to be the 'gold standard' method of establishing a diagnosis of drug hypersensitivity [72] and aim to demonstrate a drug reaction by reproducing the symptoms of allergic and in some instances non-allergic reactions. Their use is limited by the possible risk of a severe adverse reaction and should only be performed in a centre with the facilities to deal with this and by physicians experienced in drug allergy. The main indications for performing DPTs are:

1 To exclude hypersensitivity when the history is not suggestive of this (e.g. vagal symptoms following a local anaesthetic),
2 To confirm the diagnosis where the clinical history is good but *in vitro* tests and skin testing are negative or equivocal (e.g. penicillin allergy).
3 Where *in vitro* tests have limited use and skin testing is not helpful, e.g. aspirin [73].

In the contest of peri-operative anaphylaxis DPTs may be useful particularly for antibiotics, local anaesthetics, opiates and NSAIDS. The European Network for Drug Allergy (ENDA) (the interest group in drug hypersensitivity of the European Academy of Allergology and Clinical Immunology (EAACI)) has established some general guidelines for DPTs [71, 72, 74].

Specific drugs and substances involved in peri-operative anaphylaxis

Anaesthetic allergy databases show that the incidence of reactions to particular drugs reflects their level of use. Reactions to older agents such as thiopentone have fallen, whereas reactions to more modern drugs, such as rocuronium, have increased and the level of use of a drug needs to be known before any inference can be drawn about an apparently high level of allergy [75]. Almost all the drugs and substances to which patients are exposed perioperatively have been known to cause allergic reactions. There are a number that deserve closer consideration and a discussion of these follows.

Neuromuscular blocking agents (NMBAs)

NMBAs such as suxamethonium, atracurium and rocuronium, are consistently implicated as the group of anaesthetic drugs most likely to cause anaphylaxis. Mertes *et al*. found that 58.2% of anaesthetic-associated anaphylactic reactions reported in France over a 2 year period were caused by NMBAs [76]. Interestingly, previous exposure of the patient to a NMBA is not a pre-requisite for an IgE-mediated allergic reaction. It appears that exposure to some other drugs and environmental chemicals (e.g. cosmetics) which have quarternary ammonium ions, can cross-sensitize the patient to a NMBA. Recently, over the counter cough syrups containing pholcodine in Norway were implicated by this mechanism, producing a much higher prevalence of NMBA allergy than was seen in Sweden, where the drug was not available. As a result, pholcodine-containing cough syrups were withdrawn in Norway [77].

NMBAs can also cause anaphylaxis by a direct action on mast cells (i.e. a non-immune mechanism), causing histamine release. Atracurium and mivacurium are known to cause reactions by this mechanism [8, 28].

There is some difficulty regarding the advice to be given to a patient where skin prick testing to a NMBA has been positive. Cross-sensitivity between NMBAs is common. Harper *et al*. suggest that these patients should tell future anaesthetists to avoid all NMBAs. This can present practical difficulties for the anaesthetist and it is further suggested that if NMBAs are thought to be necessary, the patient should only receive one to which they have not developed a positive skin prick and intradermal test [28]. It is cautioned, however, that in this scenario a further reaction might occur [8], a concern qualified by a case report of anaphylaxis to cisatracurium, administered following a negative skin test result [78]

Latex

Natural rubber latex is an important cause for anaphylaxis, with most studies ranking it second to NMBAs [3, 8, 79]. However some smaller studies have found this to be less prominent [5, 80], perhaps relating to the implementation

of strategies to reduce latex exposure and a heightened awareness of this in patient pre-assessment [4]. Some key groups are at particular risk of latex allergy including health care workers, children with spina bifida, genitourinary abnormalities and those with occupational exposure to latex [81–84]. Diagnosis is by measuring sIgE levels to latex or skin prick testing. The latter has the greater sensitivity and specificity and is considered the 'gold standard' [85]. In some cases where there is a good clinical suspicion of latex allergy but skin testing and sIgE are negative, challenge testing with natural rubber latex can be performed [86]. Positive test results to latex can occur in the absence of clinical symptoms and a detailed clinical history is important in correctly interpreting these results [28]. Avoidance is the only current effective treatment, using latex free gloves and equipment [87]. Immunotherapy is also being tried with some success [88, 89].

Antibiotics

Antibiotics are a common cause for peri-operative anaphylaxis. They were reported as a cause for 15% of reactions in France [45, 76]. A much higher incidence was identified in a smaller study in Spain with 44% [80], while it accounted for 8.6% in a UK study [5]. Of the antibiotics identified, penicillins and cephalosporins are the commonest (70%). Diagnosis of penicillin allergy should combine sIgE measurement and skin testing (skin prick and intradermal). Both are highly specific but not sufficiently sensitive. A recent study looking at sIgE to penicillin showed that the specificity determined by fluoroenzyme-immunoassay (FEIA CAP-System®, Phadia, Uppsala, Sweden) ranged from 83.3% to 100% and sensitivity from 0% to 25% [57]. Skin testing has an improved sensitivity of 50–70% and similar high specificity of 97–99% [70, 90, 91]. Importantly a number of studies have demonstrated that in patients with a clear history of an acute allergic reaction to penicillins, a significant number had negative sIgE and skin tests but were positive by DPTs (30.7% [72], 11% [90] and 14.8% [92]). Therefore DPTs in patients with a clinical suspicion of β-lactam allergy are recommended if sIgE and skin testing prove negative.

The cross reactivity between penicillins and cephalosporins is due to their common β-lactam ring [93]. Small groups such as the methylene group, which makes up only a small part of the different side-chains on benzylpenicillin and cephalosporins, have been implicated in cross reactivity [94]. Also the structure of the side chain of the β-lactam ring is important in determining reactivity. The first generation cephalosporins and cefamandole share a similar side chain with penicillin and amoxicillin. It has been suggested from a recent meta analysis that patients who are allergic to penicillin or amoxicillin have a higher incidence of allergic reactions to first generation cephalosporins and cefamandole, but not with second and third generation cephalosporins [8, 95]. The R1 side chain, which is shared by penicillins and cephalosporins, seems to play a dominant role in determining the specificity of immunologic reactions to cephalosporins. Thus, penicillin can be administered safely to patients allergic to cephalosporins with a negative skin test result to penicillin determinants [96].

Other antibiotics associated with peri-operative anaphylaxis include vancomycin [80, 97]. Particularly rapid administration can result in life threatening non-allergic reactions. This is thought to be mediated by inducing direct histamine release and myocardial depression. Anaphylactic reactions from vancomycin occur rarely with demonstrated skin test positivity. Skin test positivity may be useful in distinguishing infusion rate associated non-allergic reactions from anaphylaxis [98].

Local anaesthetics

Local anaesthetics are frequently used during general anaesthesia but true reactions are rare. There are two main families of local anaesthetics:

1 Benzoic ester group comprising benzocaine, chlorprocaine, cocaine, piprocaine, procaine, propoxycaine and tetracaine.
2 Amide group comprising aromatic amides, articaine, bupivacaine, dibucaine, etidocaine, lidocaine, mepivacaine and prilocaine and the thiophenic amide alphacaine.

Most local anaesthetic reactions are attributable to reactions unrelated to the drug itself, such as hyperventilation and vaso-vagal attacks. Additionally other components present with the anaesthetic such as epinephrine, sulphites, parabens and antibiotics may be the culprit.

There are no available *in vitro* tests for local anaesthetics. Diagnosis is by skin prick tests (these are generally negative) and intradermal testing (false positive intradermal tests are associated with neat and 1/10 dilutions of the pure concentration). The gold standard is challenge testing with subcutaneous administration of graded volumes of the working strength drug. There have been case reports of allergic reactions to the amide local anaesthetics mepivacaine [99] and benzocaine [100] but these are very rare.

Opioids

Anaphylaxis due to opioids is very rare. Opiates, including morphine, codeine and synthetic opioids such as pethidine can cause direct mast cell degranulation without the presence of specific IgE antibodies [101]. Studies have demonstrated cutaneous mast cell release of histamine after stimulation by morphine but mast cells isolated from other tissues (lung, heart, gastrointestinal) and also

basophils do not [102, 103]. There are rare reports of IgE antibodies to morphine and codeine being detected in patients with opiate associated anaphylaxis[104]. Although some centres test for opiate allergy by skin prick testing, in view of its ability to induce positive skin tests in normal control subjects, this method of testing is not helpful and DPTs should be considered [105]. The synthetic opioids fentanyl, alfentanil and remifentanil are very rarely associated with anaphylaxis (case reports [106]). They do not directly induce histamine release and the mechanism is thought to be IgE mediated. Possible synthetic opioid associated anaphylaxis can be investigated by skin and intradermal testing [107,108].

Chlorhexidine

Chlorhexidine is a biguanide antiseptic and disinfectant, which is active against a broad spectrum of organisms, including bacteria, mycobacteria, viruses and fungi. Chlorhexidine is frequently used as a skin disinfectant before surgery or invasive procedures and it is widely used in the general population in mouthwashes or for disinfection of minor scratches. With this exposure, there is the potential for developing allergy to chlorhexidine, possibly similar to the association of pholcodine in cough mixture and NMBA allergy. A number of cases of anaphylaxis associated with chlorhexidine have been reported [109]. Particularly relevant are those associated with chlorhexidine-bonded central venous catheters [32, 110–113] and the use of urinary catheter lubricant [114–117]. The mechanism is IgE mediated mast cell /basophil degranulation and diagnosis is by measuring IgE to chlorhexidine (C8, CAP-FEIA system (Phadia)), skin and intradermal testing [118].

Dyes

Patent blue V and isosulphan blue belong to the group of triarylmethan dyes. They share the same formula. However, patent blue V has an additional hydroxyl group at position 5 [119]. Both dyes are used as tracers in lymphatic mapping for sentinel node biopsy (SNB) and are associated with peri-operative anaphylactic reactions in up to 2.7% of patients. Allergic or adverse reactions specificially to to isosulphan blue dye have been reported in 0.7–1.9% of patients undergoing SNB [120–123]. In most cases, there is no evidence for previous medical exposure. Sensitization may however develop form the widespread use of such dyes in cosmetics and other everyday life objects [124, 125]. An anaphylactic (IgE mediated) mechanism has been proposed for patent blue V [126], while for isosulphan blue, both mechanisms have been proposed [123]. Investigation of possible reactivity is by skin and intradermal testing [127]. Methylene blue is rarely involved in anaphylaxis and may be an alternative [127].

Colloids

Colloids are plasma expanders used to intravascular fluid volume. They come in various forms including albumin, dextran, hetastarch and gelatine. A French study looking at reactions associated with colloids demonstrated higher propensity to cause a reaction with gelatines and dextrans (0.35% and 0.27% of administrations), with a much lower frequency with albumin and hetastarch (0.1% and 0.06% of administrations) [128]. As a cause for peri-operative anaphylaxis, colloids were found to be responsible in 4%, with gelatine accounting for 95% of these (the other 5% being hetastarch) [76]. Specific IgE tests are available for gelatine, while skin prick and intradermal testing are useful in the diagnosis of gelatine and the other colloid associated reactions [7, 56, 128, 129].

Protamine

Protamine sulphate is an alkaline polypeptide used mainly to reverse the anticoagulant effect of heparin. Although relatively safe, significant adverse reactions have been reported, with an incidence varying from 0.06% to 10.6% [130, 131]. The mechanisms are thought to involve both allergic and non-allergic anaphylaxis, with IgE and IgG antibodies being detected to protamine [132, 133]. Other mechanisms include the generation of anaphyatoxins and prostanoids, either from protamine-heparin complexes or complement-fixing antiprotamine IgG antibodies [134]. Some risk factors have been reported in those who have had a previous vasectomy and patients with fish allergy (commercial protamine is made from the sperm of salmon), although evidence for this limited to case reports [135–137]. Previous exposure to protamine is a more significant risk factor (this includes diabetics on protamine containing insulin preparations [138–140]). SpIgE tests are available for protamine and diagnosis can also be be made by skin testing [141].

Hypnotics and inhalant agents

Of the hypnotic agents used anaphylactic reactions are more often seen with thiopental and propofol, although as a group hypnotics are a rare cause [142–144]. Diagnosis is by skin and intradermal testing, although a RAST method for detecting IgE to thiopentone has been described [143]. There are no documented cases of inhalational agents (e.g. isoflurane, sevoflurane) causing anaphylaxis.

Conclusions

Peri-operative anaphylaxis remains an important cause of morbidity and mortality during anaesthesia. The common

agents are NMBAs, latex and antibiotics. However most drugs given and a number of surgery associated agents, e.g. chlorhexidine, are an important associated cause. Important in the management is the recognition that the adverse event could be an allergic reaction on clinical grounds and checking for a raised tryptase. Appropriate referral to a unit experienced in investigation of peri-operative anaphylaxis is important. Although *in vitro* testing for possible agents is useful the lack of sensitivity means patients often require formal skin intradermal and DPTs to identify the possible agent and also decide which agents are safe alternatives.

Competing Interests

There are no competing interests to declare.

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